Amendments to the Specification:

Please replace the paragraph beginning at page 18, line 25, with the following:

A sequence variation in the CYP3A5 gene wherein an Adenine (A) in intron 3 ~~at the position corresponding to nucleotide 22,893 GENBANK sequence accession no. AC005020 (also depicted herein as nucleotide 23 of SEQ ID NO:73 of Figure 3)~~ is altered to a Guanine (G) at the position corresponding to nucleotide 22,893 GENBANK sequence accession no. AC005020 (also depicted herein as nucleotide 23 of SEQ ID NO:73 of Figure 3) ~~in this same position in~~ is one of the polymorphisms identified herein. This polymorphism leads to the expression of a truncated CYP3A5 protein with little or no catalytic activity.

Please replace the paragraph beginning at page 20, line 7 with the following:

FIGURE 3 depicts a mismatch primer (SEQ ID NO:33) for *CYP3A5*3* (SEQ ID NO:37) versus *CYP3A5*1* (SEQ ID NO:38) genotyping. The mismatch primer generates a Tru9 I/MseI restriction site on amplification of *CYP3A5*1* genotype nucleic acid. The ~~normal sequence of~~ *CYP3A5*3* sequence comprising C and not the mismatch T

is depicted as SEQ ID NO:73.

Please replace the paragraph at page 20 beginning at line 16 with the following:

FIGURE 5 depicts a mismatch primer (SEQ ID NO:34) for *CYP3A5*6* (SEQ ID NO:39) versus *CYP3A5*1* (SEQ ID NO:40) genotyping. The mismatch primer generates a Tru9 I/MseI restriction site on amplification of *CYP3A5*6* genotype nucleic acid. The ~~normal sequence of *CYP3A5*6*~~ *CYP3A5*1* sequence comprising A and not the mismatch T is depicted as SEQ ID NO:74.

Please replace the paragraph beginning at page 32, line 11 with the following:

The step (b) may be performed utilizing any method of amplification, including polymerase chain reaction (PCR), ligase chain reaction (Barany, F. (1991) Proc. Natl. Acad. Sci. 88:189-193), rolling circle amplification (Lizardi, P.M. et al. (1998) Nature Genetics 19:225-232), strand displacement amplification (Walker, G.T. et al. (1992) Proc. Natl. Acad. Sci. 89:392-396) or alternatively any means or method whereby concentration or sequestration of sufficient amounts of the cytochrome P450 3A5

(*CYP3A5*) nucleic acid for analysis may be obtained. The primers for use in amplification of at least the intron region and/or the exon 7 region of *CYP3A5* may be selected and utilized by the skilled artisan employing the sequence of cytochrome P450 3A5 (CYP3A5) as available at the National Center for Biotechnology Information (NCBI) ncbi with the extension nlm.nih.gov of the world wide web as GENBANK entry AC005020, portions of which are depicted in ~~normal~~ sequences of Figures 3 and 5 as SEQ ID NO:73 and 74, respectively, the complete sequence of *Homo sapiens* BAC clone Gs1-259H13 (Sulston, J.E. and Waterston, R. (1998) Genome Res. 8(11), 1097-1108). This particular sequence was utilized in the design and sequence of primers exemplified herein. In addition, GENBANK entry L26985 which sequence was published by Schuetz et al. (Schuetz, J. et al. (1995) Biochem Biophys Acta 1261:161-165). This sequence was originally described as a CYP3A5 pseudogene, but is actually a spliced variant mRNA, similar to the CYP3A5*3 allele product described herein. Particular exemplary primers are provided herein and include oligonucleotide primers having the sequence set out in SEQ ID NOS: 16, 24-27 and 30-32. Based on the sequence of the mutant alleles provided herein, PCR primers are constructed that are complementary to the region of the mutant allele encompassing the point mutation. A primer consists of a consecutive sequence of

polynucleotides complementary to any region in the allele encompassing the position which is mutated in the mutant allele. The size of these amplification/PCR primers range anywhere from five bases to hundreds of bases. However, the preferred size of a primer is in the range from 10 to 50 bases, most preferably from 15 to 35 bases. As the size of the primer decreases so does the specificity of the primer for the targeted region. Hence, even though a primer which is less than five bases long will bind to the targeted region, it also has an increased chance of binding to other regions of the template polynucleotide which are not in the targeted region and do not contain the polymorphic/mutated base. Conversely, a larger primer provides for greater specificity, however, it becomes quite cumbersome to make and manipulate a very large fragment. Nevertheless, when necessary, large fragments are employed in the method of the present invention. To amplify the region of the genomic DNA of the individual patient, primers to one or both sides of the targeted position, for instance the third intron (intron 3) and particularly the A/G point mutation at nucleotide 22,893 (relative to GENBANK AC005020; also depicted herein as nucleotide 23 of SEQ ID NO:73 of Figure 3), and also the position in exon 7 and particularly the G/A point mutation at nucleotide 30,597 (relative to GENBANK AC005020; also depicted

herein as nucleotide 29 of SEQ ID NO: 74 of Figure 5), are made and used in a PCR amplification reaction, using known methods in the art (e.g. Massachusetts General Hospital & Harvard Medical School, Current Protocols In Molecular Biology, Chapter 15 (Green Publishing Associates and Wiley-Interscience 1991) and as particularly exemplified herein.

Please replace the paragraph beginning at page 36, line 1, with the following:

Other rapid pharmacogenetic single nucleotide polymorphism (SNP) screening technologies which can be employed and are contemplated as suitable for step (c) currently exist and could be utilized by the skilled artisan to identify or characterize the *CYP3A5*1*, *CYP3A5*3* and *CYP3A5*6* alleles and particularly the nucleotide 22,893 (relative to GENBANK AC005020; also depicted herein as nucleotide 23 of SEQ ID NO:73 of Figure 3) and nucleotide 30,597 (relative to GENBANK AC005020; also depicted herein as nucleotide 29 of SEQ ID NO: 74 of Figure 5) SNPs. Various detection methodologies are presently available or offered by commercial companies, including Aclara Biosciences, Orchid Biosciences, Qiagen Genomics, PPGX, and Affymetrix. Exemplary such SNP detection methodologies, particularly those of Orchid Biosciences, are

provided in United States Patent Numbers 6,013,431, 6,004,744, 5,952,174 and 5,939,291, which are incorporated herein by reference in their entirety. Qiagen Genomics utilizes a Masscode system for SNP genotyping, whereby a mass spectrometer is utilized to image/detect Masscode tags attached to DNA molecules via a photochemical linker. A mass-tagged system for SNP detection is also provided by Fei and Smith (Fei Z. and Smith, L.M. (2000) Rapid Comm Mass Spectrom 14 (11):950-959). Multiplex chip or flow cytometry systems for parallel genotyping may also be utilized, as described by Affymetrix and Axys Pharmaceuticals (Fan, J.B. et al (2000)Genome Res 10(6):853-860; Armstrong, B. et al (2000) Cytometry 40(2):102-108).

Please replace the paragraph beginning on page 41, line 11, with the following:

In a particular aspect, the invention provides a method for detecting the presence or activity of cytochrome P450 3A5 (CYP3A5), wherein said cytochrome P450 3A5 (CYP3A5) is measured by:

(a) isolating nucleic acid from said subject;

(b) amplifying a cytochrome P450 3A5 (CYP3A5) PCR fragment from said nucleic acid, which includes at least intron 3, thereby obtaining an amplified fragment; and

(c) sequencing the amplified fragment obtained in step (b), thereby determining the cytochrome P450 3A5 (CYP3A5) intron 3 genotype of said subject; wherein the detection of ~~a G~~ an A nucleotide at nucleotide 22,893 of GENBANK sequence accession no. AC005020 (also depicted herein as nucleotide 23 of SEQ ID NO:73 of Figure 3); indicates the presence or activity of said cytochrome P450 3A5 (CYP3A5) in said sample.

Please replace the paragraph beginning at page 43, line 15, with the following:

In a particular embodiment, the present invention includes a diagnostic assay for determining cytochrome P450 3A5 (CYP3A5) genotype of a subject which comprises

(a) isolating nucleic acid from said subject;

(b) making a first and a second PCR primer wherein

(i) the first PCR primer is complementary to exon 7 and introduces a base change in the PCR product adjacent to or near the point mutation at nucleotide 30,597 of GENBANK accession no. AC005020 (also depicted herein as nucleotide 29 of SEQ ID NO:74 of Figure 5), such that a restriction site is generated in the presence of a particular nucleotide at nucleotide 30,597; and

(ii) the second PCR primer is complementary to a region 3' to

the ~~intron 3~~ exon 7 nucleotide 30,597 GENBANK accession no. AC005020 (also depicted herein as nucleotide 29 of SEQ ID NO:74 of Figure 5);

(c) amplifying the sequence in between the first and the second primers; thereby obtaining an amplified fragment; and

(d) treating the amplified fragment obtained in step (c) with a restriction enzyme in its corresponding restriction buffer to detect presence or absence of a point mutation at nucleotide 30,597, thereby determining the cytochrome P450 3A5 (CYP3A5) genotype of said subject.

Please replace the paragraph beginning at page 45, line 25, with the following:

In a particular aspect, the invention provides a method for detecting the presence or activity of cytochrome P450 3A5 (CYP3A5), wherein said cytochrome P450 3A5 (CYP3A5) is measured by:

(a) isolating nucleic acid from said subject;

(b) amplifying a cytochrome P450 3A5 (CYP3A5) PCR fragment from said nucleic acid, which includes at least exon 7, thereby obtaining an amplified fragment; and

(c) sequencing the amplified fragment obtained in step (b), thereby determining the cytochrome P450 3A5 (CYP3A5) exon 7 genotype of

said subject; wherein the detection of ~~an A~~ a G nucleotide 30,597 of GENBANK sequence accession no. AC005020 (also depicted as nucleotide 29 of SEQ ID NO:74 of Figure 5) indicates the presence or activity of said cytochrome P450 3A5 (CYP3A5) in said sample.

Please replace the paragraph beginning at page 48, line 4, with the following:

In a particular embodiment, the first PCR primer in a test kit of the present invention introduces a *Tru9I/~~MspI~~MseI* restriction site in the presence of an A nucleotide at nucleotide 22,893 of GENBANK sequence accession no. AC005020 (also depicted as nucleotide 23 of SEQ ID NO:73 of Figure 3).

Please replace the paragraph beginning at page 79, line 20, with the following:

We developed a mismatched PCR-RFLP based method to characterize the *CYP3A5*1*, *CYP3A5*3*, *CYP3A5*6* polymorphism suitable for large scale screening and clinical testing applications. To distinguish the *CYP3A5*1* and *CYP3A5*3* alleles, nested PCR is performed using a mismatched forward primer 5020_22871 (f)(5'-TAAAGAGCTCTTTTGTCTTTTA-3')(SEQ ID NO:33) and the reverse primer 5020_23205 (r)5'-CATTCTTTCACTAGCACTGTTC-3' (SEQ ID NO:27). The

mismatched forward primer introduces a mismatch "T" (denoted underlined; SEQ ID NO: 38) ~~normal sequence of *CYP3A5*3* comprising C and not the mismatch T is depicted as SEQ ID NO:73)~~ at nucleotide 22891 of GENBANK accession no. AC005020 (nucleotide 21 ~~23~~ of SEQ ID NO:73) of all CYP3A5 alleles, but creates a unique *Tru9*I and/or *Mse*I restriction site in the *CYP3A5*1* expressor-22893A allele (TTAA), but not in the non-expressor-G allele (TTAG). Susceptibility of the PCR product to cleavage by *Tru9*I and/or *Mse*I indicates the presence of the *CYP3A5*1* allele. The sequences of the primers and the PCR-RFLP method are diagramed in **FIGURES 3** and **4**. Homozygous (*1/*1) versus heterozygous (*1/*3) individuals can be distinguished by the presence of uncleaved full length PCR product (334 bp) in heterozygotes, in addition to the smaller cleaved DNA fragments (314 bp and 20 bp).

Please replace the paragraph beginning at page 80, line 4, with the following:

To distinguish the *CYP3A5*1* and *CYP3A5*6* alleles, nested PCR is performed using a mismatched forward primer 5020_30569(f)(5'-CACAAGACCCCTTTGTGGAGAGCACTTA-3'(SEQ ID NO:34) and the reverse primer 5020_30745(r)5'-TGGAATTGTACCTTTTAAGTGGA-3' (SEQ ID NO:32).

The mismatched forward primer introduces a mismatch "T" (denoted underlined; SEQ ID NO:40) ~~normal sequence of *CYP3A5*6* comprising A and not the mismatch T is depicted as SEQ ID NO:74)~~ at nucleotide 30595 of GENBANK accession no. AC005020 (nucleotide 27 ~~29~~ of SEQ ID NO:74) in all CYP3A5 alleles, but creates unique *Tru9*I and/or *Mse*I restriction site in the *CYP3A5*6* non-expressor-30597A allele (TTAA), but not in the *CYP3A5*1* expressor-G allele (TTAG). Susceptibility of the PCR product to cleavage by *Tru9*I and/or *Mse*I indicates the presence of the *CYP3A5*6* allele. The sequences of the primers and the PCR-RFLP method are diagramed in **FIGURES 5** and **6**. Homozygous (*3/*3) versus heterozygous (*1/*3) individuals can be distinguished by the presence of uncleaved full length PCR product (177 bp) in heterozygotes, in addition to the smaller cleaved DNA fragments (151 bp and 26 bp).